nothing of relationships, for which a knowledge of the harmony and co-operation of the units which comprise it is essential. This is the real physiology of the brain, the subject on which Hughlings Jackson himself expended so much of his hardest thinking. Jackson's knowledge of cortical function was inadequate, but that did not prevent him from the formulation of a majestic conception of the brain's actions. Since his day we became too engrossed by the cortex. In recent years attention has shifted back again, none too soon, to the subcortex—to the brain stem and basal ganglia—in a way that earlier generations would have recognized as a search for integration along paths fainter in their day but nevertheless familiar. The new work has come largely from the Canadian school led by Wilder Penfield and Jasper, the Americans led by Ranson and Magoun and their many pupils, and also from Adrian in England and Bremer in Brussels.

Our current knowledge of the cortex and its deeper connexions has been made possible by modern technical inventions. If the conception of the centrencephalic system, to use Penfield and Jasper's term for a lower level integrating centre—a concept not, it is true, accepted by all—runs counter to Jacksonian levels, if higher levels physiologically seem to be lower anatomically, and therefore not to fit very well, we have no right to say that the proposition is necessarily wrong. It may not indeed be the last word, yet it fits well with neurosurgical clinical experience. We see the powers that reside in human minds called into being along the ancient pathways which man shares with the animals—but with a final result so different because of the immense potential cellular wealth of the cortex and the vast richness of its relays and communication systems. We see them destroyed by lesions at mid-brain level more completely than anywhere else.

This is the crux of the new plan of integration in which cortical localization has its proper and honoured place. If we no longer believe that such things as love and loyalty, tenderness and friendship and happiness, have special abodes in the brain, yet we know that some such attributes exist, fictitious as definite entities though they may be, and that they are the by-products of the harmony of body and brain.

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The annual report of the Marie Curie Memorial Foundation for 1954–5 records the continuing progress of this organization and the excellent work it is doing. Some interesting details are given of the cancer talks which were available through the Hull Phonodiary Service (see *British Medical Journal*, October 2, 1954, p. 802). Three recorded talks were made lasting for 2¼ minutes each. The first was on signs and symptoms, the second on methods of treatment, and the third on progress of research. The first talk was available to subscribers on the Hull telephone exchange for 12 weeks, and the average number of those who listened to the talk each week was 429. Thirty-two trunk calls were made during this period from inquirers living outside Hull. The second talk was available for 15 weeks, and 369 people listened to it on an average each week. The third talk was apparently not so popular, the average number of listeners per week being 221. It is considered that the main advantages of this method of health education by telephone are that the person making the inquiry remains anonymous and that it is possible to check the number of inquiries made without destroying this anonymity.

FLUOROSIS IN NALGONDA DISTRICT, HYDERABAD-DECCAN

BY

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Fluorine is one of the trace elements normally present in the body, and, in small amounts, exerts a beneficial influence on the enamel of teeth. Fluorine is found in most foodstuffs and in drinking-water in areas of endemic fluorosis. Fluoridation of public water supplies has lately been undertaken in the United States, so that to-day nearly sixteen million people in the U.S.A. are drinking fluoridated water, and a marked reduction in dental caries has been noted (Ast *et al.*, 1950; Schlesinger *et al.*, 1950; Heyroth, 1951, 1952, 1953). Stones (1954) has reviewed in detail the subject of fluoridation of domestic water supplies so far as it controls dental caries.

The amount of fluorides required for industrial purposes exceeds 500 million pounds (226,796,000 kg.) (Largent and Ferneau, 1944). Industries such as mining, and the conversion of phosphate into superphosphate, a common fertilizer, and the manufacture of glass, enamel, and aluminium, expose workers to appreciable dangers of excessive fluoride intake. Industrial exposure to fluorine is now known to produce a form of osteosclerosis, to which its Danish discoverers, Møller and Gudjonsson (1932), have given the name fluorosis.

Adequate research on the industrial and experimental aspects of fluorine intoxication has been carried out in Britain, Europe, and the United States. In India the pioneer work on endemic fluorosis was done by Shortt and his collaborators (1937a, 1937b). In Hyderabad-Deccan this field has so far remained unexplored from a clinical point of view, although fluorosis is prevalent in many parts. This paper therefore proposes to bring forward in detail the various clinical features of the disease, with special reference to attendant neurological manifestations, both in human subjects and in animals.

The Investigation

The villages of Kamaguda, Yedvelli, and Yellareddyguda were chosen for investigation. These villages lie close to each other, about 50 miles from the city of Hyderabad, in the Nalgonda District. The climate is hot and in summer the temperature touches 115° F. (46.1° C.) in the shade. The average annual rainfall is 25 in. (63.5 cm.). The soil is sandy and consists of granite associated with fluorite. Work on tobacco plantations is the main occupation of the people.

The populations of Kamaguda, Yedvelli, and Yellareddyguda are 95, 813, and 1,100 respectively. The general standard of living is low, the hygienic conditions are poor, and the system of disposal of sewage is inadequate. There are 2, 13, and 84 wells respectively. Twenty-eight samples of drinking-water were analysed for their fluorine content—2 from Kamaguda, 13 from Yedvelli, and 13 from Yellareddyguda. The concentration of fluorine varied between 9.2 and 11.8 parts per million in Kamaguda, between 5.5 and 6.8 in Yedvelli, and between 2.5 and 7.5 in Yellareddyguda. The concentration of fluorine in the water used by the patients, and in the mud samples obtained from these wells, is shown in Tables I and II.

TABLE I

Place of Sampling	Temperature at Time of Sampling	Fluorine Content of Water (p.p.m.)*	
		Well No. 1†	Well No. 2†
Kamaguda	90° F. (32·2° C.)	9·2	11·0
	115° F. (46·1° C.)	9·6	11·8
Yedvelli ..	108° F. (42·2° C.)	5·5	6·5
	115° F. (46·1° C.)	5·8	6·8
Yellareddyguda ..	115° F. (46·1° C.)	5·2	6·7

* Estimated by thorium nitrate titration method.
† Well Nos. 1 and 2 are situated hardly 100 yards apart.

TABLE II

Place of Sampling	Fluorine Content of Mud Samples
Kamaguda	0·15%
Yedvelli	0·11%
Yellareddyguda	0·09%

The nutritional state of the people was poor, the diet being deficient in animal proteins, fats, calcium, and vitamins A and C, as seen from the average figures given in Table III.

Fluorosis in Animals.—Skeletal changes of an advanced degree were noticed among the cattle. Symptoms of emaciation, weakness, and laboured gait were common. The animals were reported unfit for field-work after three years in Kamaguda. Poultry is relatively resistant to fluorine intoxication (Peirce, 1940), but in Kamaguda they were affected because of the high fluorine content of water (see Discussion). The chickens had a stiff-legged gait. Within 10 months ankylosis of the knee-joints developed.

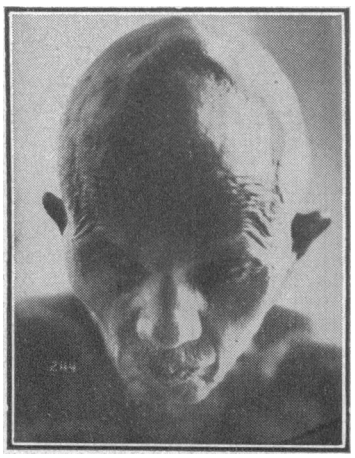

FIG. 1.—Case 18. Showing exostoses of skull.

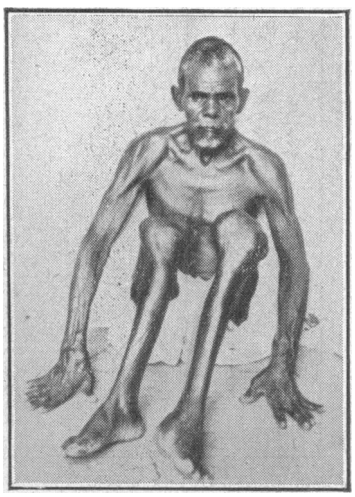

FIG. 2.—Case 19. Showing projections from tibiae and bowing of the shaft.

Physical Examination.—Thirty-two advanced cases of the disease with neurological manifestations were investigated. The important clinical features, the fluorine content of water consumed, and the duration of intoxication are shown in Table IV.

Eighth-nerve functions (audiometry and the caloric tests) were investigated in seven cases (Nos. 23, 24, 25, 26, 27, 28, and 32). A marked loss in hearing for higher frequencies resembling a degenerative lesion of the cochlea was commonly recorded. In cases with severe loss for higher frequencies the labyrinth was also sluggish in reacting to stimuli (see Discussion). The results of the investigation of the eighth-nerve functions are given in Table V.

The Dental Condition.—*Adults:* 32 adults admitted to the wards were examined dentally. Of these, 15 resided in the endemic area during the period of calcification of permanent teeth and had mottled enamel (dental fluorosis). Three patients were edentulous. The remaining 14, who had migrated from non-endemic areas after the age of 14, had normal teeth. *Children:* Dental examination was made of 110 children aged 3 to 14 years. The following grades of mottled enamel were adopted:

Mild.—White opacities or patches on the enamel; very faint yellow line across the enamel.

Moderate.—A distinct brown stain.

Severe.—Besides the well-established brown line, considerable pitting all over the enamel, sometimes with chipped-off edges.

The most commonly affected teeth were the central incisors and the first molars. The surfaces subjected to attrition showed marked lesions. Irregular areas of black pigmentation with pitting were met with only once (Fig. 3).

Mottling was rare in the age group 3 to 6 years, was evident in the age group 7 to 9 years, and was definite in the age group 10 to 14 years. Mottling of deciduous teeth, an evidence of placental and mammary transmission of fluorine, similar to that recorded by Smith and Smith (1935) and Roholm (1937), was noted only twice. The incidence

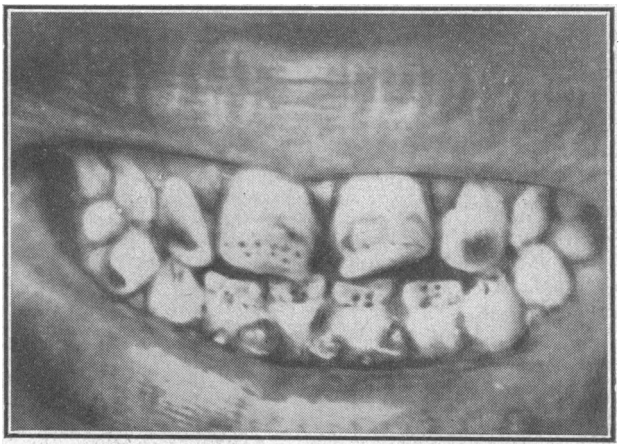

FIG. 3.—Showing irregular patches of black pigmentation on teeth, with pitting.

of mottled enamel found was proportional to the fluorine content of drinking-water. The dental changes, therefore, were similar to those described by Shortt *et al.* (1937a, 1937b), Roholm (1937), Daver (1945), Murray and Wilson (1942), Pillai (1942), Spira (1942), Venkateswarlu *et al.* (1952), and Satyanarayana Murthi *et al.* (1953).

Frequent reference has been made in the literature to the possibility that fluorine may reduce the incidence of caries in human teeth. The condition of the first molar was studied with particular attention because of the high rate of caries in it. The coexistence of mottled enamel and caries in the same molar was noted in only two cases. On the whole, the incidence of caries was very low in endemic areas.

Radiological Findings

Sclerosis of the bones was observed throughout the skeleton, similar to that described by Roholm (1937), by Shortt *et al.* (1937a, 1937b), and by the British research workers in the Fort William area of Scotland in 1949.

In the less advanced cases the cancellous bones showed accentuation of the trabecular structure due to their thickening. Later the trabeculae coalesced and gave an increased density to the bone, which seemed to be granular or amorphous in structure. Where the sclerosis was complete the bone appeared chalky and structureless on the *x*-ray negative. These progressive changes were best observed in the pelvis and the spine. The entire vertebral column was affected despite pronounced changes in the lumbar region. The involvement of the cervical spine was earlier and much more frequent than that previously reported (Fig. 4). Sclerosis was noted in the body, the transverse and spinous processes, and the pediculate articulations of the vertebrae. The

TABLE III

Protein:		Carbohydrates .. .. 494·9 g.	Vitamins:
Animal .. .. .. 5·2 g.	78·3 g.	Calcium .. .. 0·48 g.	Carotene .. 1,048 i.u.
Vegetable .. .. .. 73·1 ,,		Phosphorus .. .. 1·78 ,,	Vitamin A .. .. 176 ,, 1,224 i.u.
Fats:		Iron .. .. .. 39·1 mg.	,, B_1 .. 648 ,,
Animal .. .. .. 8·9 g.	28·8 g.	Calories 2,618	,, C .. .. 23 mg.
Vegetable .. .. .. 19·9 ,,			

TABLE IV

Case No.	Sex and Age	Fluorine Content of Water (p.p.m.)	Duration of Intoxication (Years)	Age at Onset of Symptoms	Symptoms		Clinical Features
					Early	Late	
1	M 70	11·8	16	56	Pain and stiffness of knees, ankles, and vertebral column. Paraesthesiae of all limbs. Pain in chest on deep breathing	Pain in all joints. Dyspnoea on exertion due to fixity of costo-vertebral joints. Completely rigid spine. Impotence	Generalized muscular wasting. Muscular tenderness on pressure. Completely rigid spine, K.J., A.J. brisk. Bilateral extensor plantar response. Ankle clonus. Vibration sense lost in lower limbs. Patchy anaesthesia*
2	M 30	11·8	6	27	,, ,,	Pain in all joints. Difficulty in getting up from squatting position. Impotence	Generalized muscular wasting. Muscular tenderness on pressure. Movements of lumbar spine more restricted than rest of vertebral column—extension more limited than flexion. K.J., A.J. brisk. Patchy anaesthesia
3	M 50	11·8	6	47	,, ,,	,, ,, Dyspnoea on exertion	,, ,, ,, Extensor plantar response right
4	M 43	11·8	6	40	,, ,,	,, ,,	,, ,, ,,
5	M 45	9·6	9	40	,, ,,	,, ,,	,, ,, ,, Bilateral extensor response. Impaired vibration sense lower limbs
6	M 22	11·8	1	21	,, ,,	—	—
7	M 26	9·6	8	22	,, ,,	Pain in all joints. Difficulty in getting up from squatting position	As Case 2
8	M 50	11·8	7	45	,, ,,	As Case 3	,, ,, 5
9	M 42	9·6	9	37	,, ,,	,, ,, 3	,, ,, 5
10†	F 50	—	Since birth	40	Pain and stiffness of wrist, elbow, and shoulder-joints. Paraesthesia in limbs. Pain in chest on deep breathing	,, ,, 7	,, ,, 5
11	F 30	11·8	9	25	,, ,,	,,	,, ,, 5
12	F 55	11·8	6	51	,, ,,	,,	,, ,, 2
13	F 30	11·8	9	25	,, ,,	,,	,, ,, 5
14	F 24	11·8	7	21	,, ,,	,,	,, ,, 2
15	M 35	6·8	Since birth	30	Pain and stiffness of knees, ankles, and vertebral column	,, ,, 2	,, ,, 3 Bilateral extensor plantar response
16	M 40	5·8	,, ,,	34	,, ,,	,, ,, 2	As Case 3. Exostoses skull
17	M 45	6·8	,, ,,	40	,, ,,	,, ,, 2	,, ,, ,, Impaired vibration sense in lower limbs
18	M 50	6·8	,, ,,	40	,, ,,	,, ,, 1	As Case 1. Exostoses skull, Fig. 1
19‡	M 50	6·8	,, ,,		,, ,, Started soon after injury	Pain in all joints and inability to stand up	As Case 1
20	F 35	6·8	22	34	As Case 10	As Case 7	,, ,, 5
21	F 40	5·8	30	37	,, ,, 10	,, ,, 7	,, ,, 5
22	M 55	5·2	Since birth	40	Pain and stiffness of knees, ankles, and vertebral column. Paraesthesia of limbs	,, ,, 1	,, ,, 1
23	M 60	5·2	,, ,,	41	,, ,,	,, ,, 1	,, ,, 1
24	M 60	5·2	,, ,,	39	,, ,,	,, ,, 1	,, ,, 1
25	M 40	6·7	,, ,,	38	,, ,,	Pain in all joints. Bedridden with incontinence of urine	,, ,, 1
26	F 50	6·7	,, ,,	40	,, ,,	As Case 1	,, ,, 1
27	F 50	6·7	40	49	,, ,,	,, ,, 7	,, ,, 2
28	F 52	6·7	42	49	,, ,,	,, ,, 7	,, ,, 5
29§	M 40	Not known	Since birth to the age of 30, when he migrated to Hyderabad City	25	,, ,,	,, ,, 7	,, ,, 2
30§	M 60	,, ,,	Since birth	40	,, ,,	,, ,, 1	,, ,, 1
31§	M 50	,, ,,	,, ,,	39	,, ,,	,, ,, 2	,, ,, 2
32§	F 22	,, ,,	,, ,,	Started 3 months ago	,, ,,	—	—

* The nerves were not thickened, and the ear clippings were negative for Hensen's bacillus.

† Resided in another endemic area since birth (Dever Kunda—fluorine content of water consumed not known) until a year ago, when she migrated to Kamaguda. She had mottled enamel—an undisputed evidence of fluorine intoxication.

‡ At the age of 20 injured his right knee. Gradually projections from the tibiae appeared, with bowing of the shaft (Fig. 2). For the past six years has been unable to stand up.

§ Admitted to the wards primarily for ailments other than those of fluorosis.

TABLE V.—*Investigation of the Eighth Nerve in Fluorosis*

Case No.		Audiogram 128	256	512	1,024	2,048	4,096	8,192	Labyrinthine Reaction Caloric
23	R A	60	60	45	40	45	55	40	H 60–75 sec.
	R B			20	20	35	10	10	C 53–105 ,,
	L A	40	40	40	30	60	55	25	H 67–85 ,
	L B		35	25	20	35	35	25	C 55–110 ,,
24	R A	50	40	35	40	35	40	30	H 35–120 ,,
	R B		10	0	5	30	55	25	C 57–95 ,,
	L A	35	30	35	40	30	25	25	H 60–100 ,,
	L B		0	0	5	30	25	0	C 60–95 ,,
25	R A	25	30	25	30	45	55	30	H 55–105 ,,
	R B			10	5	25	35	30	C 35–100 ,,
	L A	25	20	20	25	30	35	20	H 90–105 ,,
	L B			10	10	35	50	30	C Nil
26	R A	Nil	75	65	45	55	40	65	H 50–100 ,,
	R B			0	10	35	40	30	C 55–95 ,,
	L A	45	50	40	55	55	45	40	H 50–90 ,,
	L B			0	5	30	50	35	C 55–90 ,,
27	R A	45	45	50	20	30	30	20	H 65–110 ,,
	R B			0	10	35	50	45	C 70–100 ,,
	L A	40	30	20	30	40	40	40	H 65–100 ,,
	L B			5	5	20	45	Nil	C 70–100 ,
28	R A	45	40	40	65	55	55	Nil	H 40–120 ,,
	R B			25	50	50	55	,,	C 50–110 ,,
	L A	45	45	45	60	55	95	,,	H 40–115 ,,
	L B			40	40	55	60	,,	C 55–95 ,,
32	R A	65	55	65	60	65	65	70	H 25–130 ,,
	R B			30	50	60	60	55	C 25–135 ,,
	L A	50	45	45	55	40	35	65	H 25–140 ,,
	L B			30	15	20	50	50	C 25–130 ,,

R=Right. L=Left. A=Air. B=Bone. H=Hot water, 44° C. C=Cold water, 30° C.

margins of the transverse and spinous processes were irregular owing to new bone formation. The intervertebral ligament showed calcification (Fig. 5, A). Lipping of the bodies of the vertebrae, especially in the lumbar region, was common. The beaklike exostoses were mostly from the lower margins (Fig. 5, B). Lipping would be expected in any population containing a fair proportion of individuals of the older age groups. In contradistinction to the lipping of osteoarthritis in the aged, the cases under review showed sclerosis of the vertebral bodies, so characteristic of fluorosis. In the thoracic region the costo-vertebral articulations added an extra density and irregularity to the lateral margins of the spine.

In the pelvis the sclerosis was more pronounced around the sacro-iliac and hip-joints. The capsule of the hip-joint was found calcified. The exostoses from the iliac spine were less marked. The crest of the ilium, the ischial tuberosity, and the margins of the sacrum invariably showed exostoses and, in advanced cases, ossification of ligaments attached to them. The acetabulum showed lipping, and exostoses were observed on the trochanters of the femur.

The cortical portion of the long bones was dense and thick, with a reduction of the marrow cavity due to endosteal bone formation. Periosteal bone formation was also noted, and was best observed in the areas of tendinous, fascial, and muscular attachments—for example, the interosseous membrane of the forearm (Fig. 6) and leg, the linea aspera, the deltoid tuberosity, and the lower margins of the ribs. The interosseous membrane of the forearm at the middle third

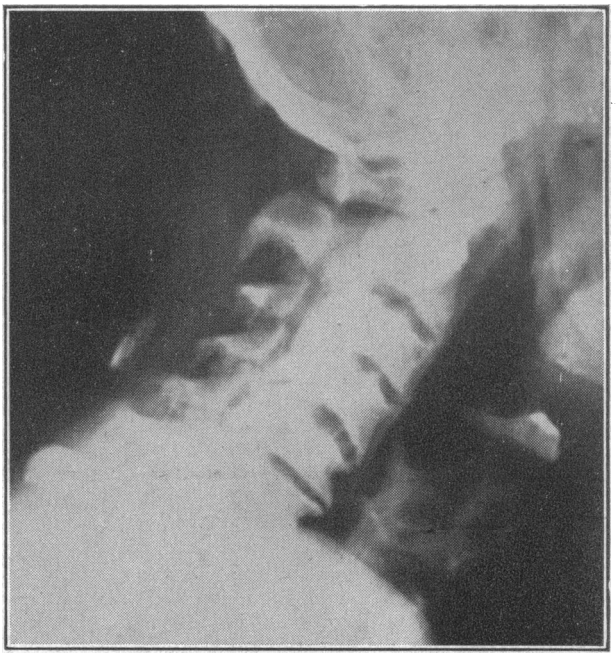

FIG. 4.—Showing involvement of the cervical spine.

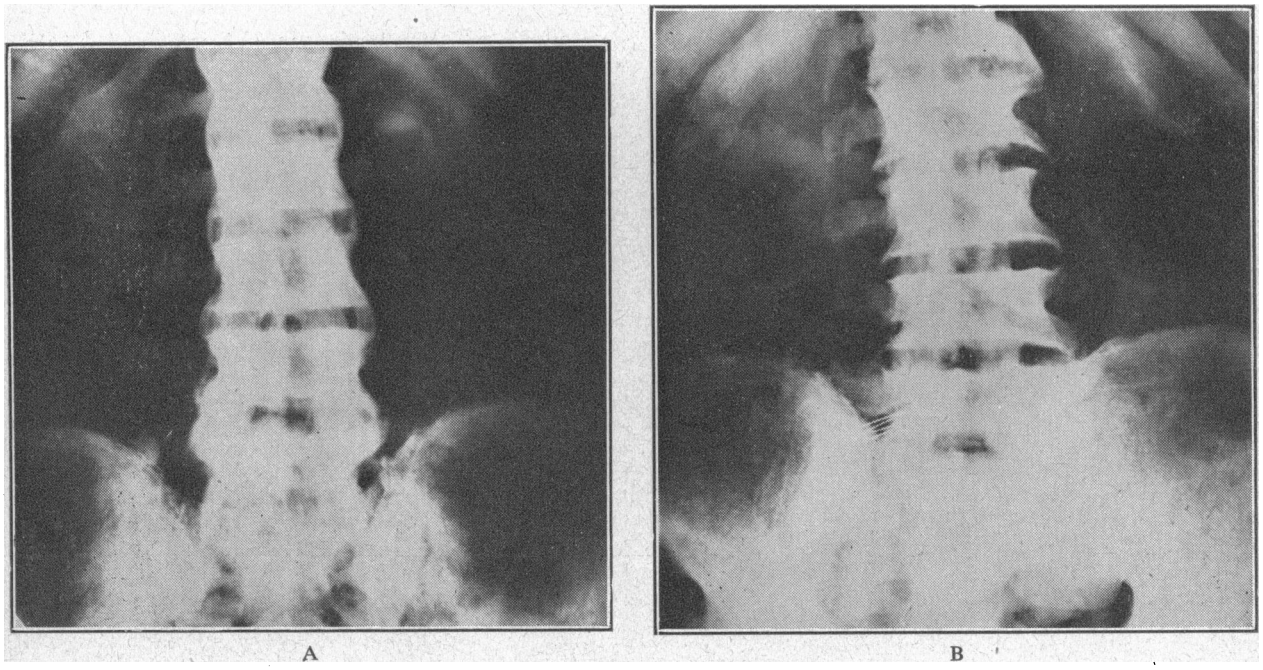

FIG. 5.—Involvement of the vertebral column, with calcification of the intervertebral ligaments.

showed ossification in advanced cases. A similar thin flake of bone was observed in the leg.

Sclerosis around the suture lines was often observed in the vault of the skull in the series reported. Shortt *et al.* did not describe definite changes in the skull. Roholm, however, has observed changes in the skull of cryolite workers. In advanced cases of the present series marked thickening was noted in the vault and the base. In Cases 18, 19, 22, and 28 the air cells were narrowed, and in Cases 17, 19, 22, and 23 the clinoid processes were thick and dense. These changes in the air cells and the clinoids have not been mentioned by others.

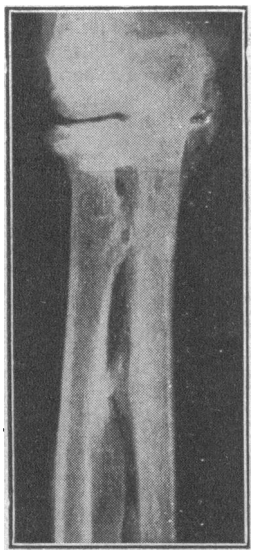

FIG. 6.—Showing periosteal bone formation of the forearm.

The degree of pathological changes varied in different parts of the same case. The changes observed in the skull had no relation to the general skeletal changes, although skull changes were more common in cases with an advanced degree of sclerosis.

Case 19 (Fig. 2) injured his right leg at the age of 20. He had a malunited fracture of the femur at the junction of the lower with the middle third. The healed bone did not show any deviation from that seen in normal cases. He had advanced bony changes. The knee-joint showed bony ankylosis, with osteophytes and sclerosis of the articular surfaces. On account of this disability he was unable to stand, and moved about with the help of his upper limbs. The bones of his hands showed pronounced sclerosis with marked lipping of articular surfaces. On the contrary, the right femur and tibia showed signs of disuse and slight arching.

The degree of osteosclerosis was found to be related to the duration of intoxication and the concentration of fluorine in the water. Physical strain was also found responsible : the greater the strain, the more pronounced were the changes observed. The changes in the hands were of an advanced nature. The changes in the skull and the cervical spine, so seldom observed by Roholm and others, were frequently encountered, a fact that could also be ascribed to the same phenomenon of strain. All the patients investigated were manual labourers and carried heavy loads on their heads. This is not a common practice in countries where the previous workers made their observations.

Haematological and Biochemical Investigations

Besides routine blood counts, urine and stool examinations, and the blood Wassermann reaction, the following investigations were made in each case : serum calcium, serum inorganic phosphorus, urinary calcium, glucose tolerance curve, blood urea, fluorine estimation of blood and of urine, fractional test meal, C.S.F. routine, including the Wassermann reaction, and the colloidal gold curve. The urea clearance test was done in 14 cases. Only the abnormal and interesting findings need be mentioned.

Blood Picture.—Most of the cases had a mild degree of anaemia. The white cell count was normal. The red cells showed no abnormality in size or shape, suggesting that the anaemia is the result of osteosclerosis narrowing the marrow cavity (confirmed by sternal puncture). The mean values for haemoglobin concentration and blood cell counts were : Hb 77% (Sahli : 100% = 14.5 g./100 ml.); red cells, 4,500,000 ; white cells 8,700).

Extensive biochemical investigations were not carried out in fluorine intoxication, although most of the research workers have reported the results of calcium and phosphorus levels. Published reports are conflicting.

Serum Alkaline Phosphatase.—The figure was above normal in all cases and was proportional to the severity of bony changes. The average was 29 K.A. units.

Urea Clearance Test.—This test (Van Slyke method) was performed in 14 cases, the clearance being maximal in 5 and standard in 9 cases. The results showed marked impairment of renal function. The mean figures for the maximum and standard clearance were 26.24 and 39.67% of the normal respectively.

Fractional Test Meal.—In many cases an extensor plantar response was elicited along with absent or impaired vibration sense, suggesting the possibility of subacute combined degeneration of the cord. In view of this, F.T.M. was done in every case. In no instance was achlorhydria encountered. The only possible explanation of these neurological manifestations could be the pressure on the cord by bony ingrowths in the spinal canal, similar to those reported by Lyth (1945).

Blood, Urinary, and Stool Fluoride Levels.—With use of the thorium-nitrate titration method, the lowest recorded figure found for blood fluorides was 0.1 and the highest 0.8 p.p.m. of whole blood. The urinary fluoride excretion varied between 1.2 and 5.8 p.p.m. Individual estimations of blood and urinary fluoride showed that the most obviously affected subjects (clinically and radiologically) had higher values. The mean values for blood and urinary fluoride were 0.34 and 2.75 p.p.m. respectively. Excretion of previously stored fluoride in urine has been reported by Largent and Heyroth (1949) and Largent (1949). Our No. 29 was a case in point. He resided in the endemic area till the age of 30, and then migrated to the city of Hyderabad, where the water is fluoride-free. The urinary fluoride level was 3.4 p.p.m. Fluoride estimation of stools was carried out thrice, with negative results.

Fluorine Content of Bones.—The bones of an affected chicken from Kamaguda, aged 10 months, were analysed. The fluorine content was 37.8 mg. per 100 g. of dry material. The bones of a control chicken of the same age, sex, and species did not contain fluorine.

Discussion

Consumption of fluorine-contaminated water gives rise to fluorosis, as has been reported from many parts of India by Shortt *et al.* (1937a, 1937b), Pandit *et al.* (1940a, 1940b), Raghavachari and Venkataramanan (1940), Pillai (1942), Daver (1945), Khan and Wig (1945), Venkateswarlu *et al.* (1952), and Satyanarayana Murthi *et al.* (1953). A few cases of fluorosis due to the use of fluorine-contaminated water were traced in Western Kweichow (China) by Lyth (1945). Sporadic reports have come from Argentina, Australia, Canada, England, Greece, Holland, Hungary, Italy, Japan, Mexico, and Spain. The remarkable uniformity of symptoms and signs in patients with skeletal fluorosis was first emphasized by Shortt *et al.* and confirmed by the present investigation.

The degree of disability and the time of onset of the symptoms of the disease were relative to the concentration of fluorine in water and to the length of time of its ingestion. In Kamaguda the concentration of fluorine in water was 11.8 p.p.m., the highest figure recorded so far in India. Symptoms of intoxication appeared in immigrants into this area in from one to four years after their arrival. At the time of the present investigation the fresh arrivals into the endemic area were free from symptoms of intoxication, whereas those who had migrated from the villages one to four years before showed marked skeletal symptoms. This finding that it takes one to four years for the symptoms to manifest themselves is at variance with that of Shortt *et al.*, who concluded that a residence of 30 to 40 years in the endemic area was required for a definite picture of skeletal fluorosis to develop. An exceptionally high fluorine content of water, excessive heat, and a poor state of nutrition are probably responsible for the early development of skeletal fluorosis in Kamaguda. The presence of signs of fluorosis in poultry, which are very resistant to fluorine, also points

to the intensity of intoxication. In Yedvelli and Yellareddyguda (where the fluorine content of water is relatively low) a much longer period of residence, similar to that described by Shortt *et al.*, was necessary before signs of intoxication appeared. The poultry were unaffected in these villages.

The severity of the disease has a definite relation to the meteorological factors (for example, temperature), and to the economic and nutritional status of the people (Pandit *et al.*, 1940a, 1940b; Daver, 1945). Hot weather not only increases the water intake but also increases the concentration of fluorine (see Table I) and ingestion of an abnormal amount of sediment. The protective action of calcium against the toxic action of fluorine has been noted by Ranganathan (1941) in rats, by Majumdar and Ray (1946) in bulls, and by Pandit and Narayana Rao in monkeys. Pandit and Narayana Rao and Wadhwani (1952) found that administration of vitamin C lessened the severity of fluorosis in monkeys. The state of nutrition in the villages under review was poor. The diet was deficient in animal proteins, fats, calcium, and vitamins A and C. These factors might have been responsible to a certain extent for the severity of bony changes in these villages. Lower temperature and better economic conditions are undoubtedly factors responsible for the absence of crippling disabilities in countries such as Britain and the United States.

The degree of disability was also related to physical strain. It was most pronounced in manual labourers. Subjects pursuing sedentary occupations, such as the local village administrative officials and schoolteachers, had less severe symptoms although they were utilizing the same sources of water supply. Pain and stiffness were more severe in the joints used most by the individual—for example, the wrists, shoulders, and neck in the females, who were mostly engaged in household work; and the lumbar spine and the joints of the lower limbs in the males working in the fields.

Children, apart from dental changes, do not suffer from the ill effects of fluorine. Probably the growing tissues are somehow able to deal with the fluorine ingested. Shortt *et al.* (1937a, 1937b) suggested a probable cumulative effect of fluorine which continues until the subject is 30 or 40 years of age, when symptoms of skeletal fluorosis begin to appear. The former view seems plausible. In Kamaguda two groups were selected for comparison. The first group comprised children who resided in the village during the period of calcification of teeth and had mottled enamel. The second group consisted of adults who had settled down in the village after the age of 30. The length of exposure to fluorine was identical in both groups. It was noted that, apart from mottled enamel, the children did not show any evidence of skeletal fluorosis. On the contrary, the adults had developed frank manifestations of skeletal fluorosis.

While studying the aetiology of otosclerosis, Spira (1943) observed a pronounced similarity in the cross-section of the petrous portion of the temporal bone of otosclerotic subjects and in the mottled teeth of fluorine intoxication. He suggested a possible relationship between the two. No dogmatic statement, however, can be made, since the number of cases in which the eighth-nerve functions were tested is only seven in the series reported, and there is no support from any necropsy data. However, our findings (Table IV) do not suggest otosclerosis, for the hearing-loss was for both air and bone conduction. Even in the youngest patient, aged 22 (Case 32), there was a preponderance of loss for higher frequencies, which is against otosclerosis. The findings suggest that the degenerative lesion may be due to pressure of new bone formation around the organ of Corti. This particular aspect of fluorine intoxication requires further investigation.

The reading of the blood fluoride level has been persistently low in the series reported. Machle, Scott, and Largent (1942) studied the normal fluoride balance in human volunteers in America. They found that in temperate climates the excretion of fluoride in the sweat was very small; but they expressed the opinion that under conditions of excessive sweating the possibility of definite loss of fluoride must be considered. McClure and collaborators (1945) indicate that fluoride is excreted by the skin, in some instances, in quantities that equal those excreted by the kidneys. The intense heat of Nalgonda, and the hard manual labour the patients went through, must have caused a considerable loss of fluoride in the sweat. Unfortunately an estimation of the amount of fluoride lost by this route could not be made. Increased excretion of fluoride by the skin on the one hand, and, on the other, rapid deposition in the bones as a result of nutritional deficiencies, seem to give a possible explanation for the low blood-fluoride values in the cases under discussion.

Urinary excretion of previously stored fluoride can continue for a fairly long period (Largent and Heyroth, 1949; Largent, 1949). Excretion of previously stored fluoride was recorded in our Case 29, in which the urinary fluoride level was 3.4 p.p.m. 10 years after the patient had left the endemic area.

Summary

Details of investigations of 32 cases of skeletal fluorosis with neurological manifestations are described.

The results of the eighth-nerve functions are reported.

The probable factors responsible for early skeletal changes in patients from Kamaguda are discussed.

A case is described in which excretion of previously stored fluoride continued in the urine at a high level 10 years after the endemic area had been left.

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